REMARKS

Claims 13 and 16-22 are pending in the present application. Claims 13 and 16-22 stand rejected. Claims 13 and 21 are cancelled and claims 16-20 are amended herein. With entry of the amendments herein, claims 16-20 and 22 are under consideration.

Claim 16 is rewritten in independent form and amended to enhance clarity. Claims 17-20 have been amended solely to correct dependency. Support for claims 16-20, as amended, is found throughout the application and in the claims as originally filed. For example, support for the amendments to claim 16 can be found throughout the examples of the specification. No new matter is added by way of the amendments to the claims.

35 U.S.C. § 103(a)

Claims 16-20 and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Stoute in view of Davis, Krieg and/or Raz (all of record). To the extent that the rejection is maintained with respect to the amended claims, Applicants traverse.

Claim 16 (and claims 17-20 and 22 dependent therefrom) recite a combination vaccine that includes a particular antigen that is a fusion protein made up of a malarial circumsporozoite protein and HBsAG (RTS,S or RTS,S*) in a specific formulation that the Applicants found especially effective for eliciting both humoral and T cell-mediated immune responses. In addition to the malarial antigen fusion protein, the claimed compositions contains two different adjuvants specifically selected based on their beneficial properties in combination with the malarial antigen fusion protein. The improved immunogenicity of this particular formulation is illustrated in the experimental examples section of the as-filed specification, and is summarized in the conclusion on page 14, lines 24-27:

> Immunization with RTS,S in combination with CpG induces immune responses in non-human primates. After two immunizations CpG alone induces low level HBsAG-specific antibodies, while CpG combined with alum induces high titer antibodies as well as vigorous lymphoproliferative and IFN-γ responses.

Applicants agree that Stoute teaches the particular RTS,S malarial fusion protein antigen component of the claimed combination vaccines. For example, Stoute teaches that a malarial fusion protein antigen in combination with alum and MPL adjuvants is capable of eliciting a weak immune response and requires at least three doses of vaccine to elicit a

detectable response. However, as the Examiner admits, Stoute does not teach the particular claimed formulation, which combines the RTS,S or RTS,S* antigens with a combination of CpG and alum adjuvants.

The Examiner alleges nonetheless that taken in combination with, *e.g.*, Davis, that it would have been obvious to one of skill in the art to produce a combination vaccine formulated to contain the particular antigen of Stoute, with both an alum adjuvant and a CpG oligonucleotide. The Examiner bases this conclusion on the alleged suggestion that a CpG oligonucleotide is an effective adjuvant in combination with, *e.g.*, a parasite antigen, along with the suggestion in Davis that synergistic adjuvants be included in the vaccine.

Applicants submit that neither of these suggestions can be generalized to the specific malarial antigens and formulations currently claimed. For example, Davis provides experimental evidence suggesting that a single dose of recombinant HBsAg antigen in combination with a CpG oligonucleotide adjuvant yields an antibody titer 60-fold higher than preimmune serum. (column 37, line 13). In contrast, Fig. 2 of the as-filed specification demonstrates that RTS,S antigen in combination with a CpG oligonucleotide induces a low level antibody response. Comparison of the immune stimulatory effects of a CpG oligonucleotide with these different (but related) antigens illustrates the lack of predictability in determining appropriate adjuvants for particular antigens. These results emphasize that the efficacy of CpG oligonucleotides as adjuvants in a combination vaccine containing an RTS,S (or RTS,S*) antigen could not have been predicted with reliability as of the filing date of the subject application.

Similarly, it is impossible to predict with any certainty which combinations of adjuvants produce a superior immune response. As of the filing date of the subject application, there was no predictable way of foreseeing which particular adjuvants would be especially advantageous when combined with a particular antigen. As described in Stoute, for example, the combination of alum and MPL adjuvants, both of which are strong adjuvants in other contexts, yields only modest immune stimulation when combined with the RTS,S antigen. Thus, a skilled practitioner seeking to find strong adjuvants that act together in the context of a combination vaccine containing an RTS,S antigen (or an RTS,S* antigen) would have no reasonable expectation that the combination of a CpG oligonucleotide and an alum adjuvant would achieve such superior results in a combination vaccine as has been

demonstrated by the data in the patent application, and specifically the strong antibody, lymphoproliferative and IFN-γ responses.

Because a skilled practitioner, even one motivated to produce a malarial vaccine capable of eliciting an immune response in a subject, could not reasonably expect that the particular claimed combination of RTS,S or RTS,S* antigen and CpG and alum adjuvants would act together to elicit the aforesaid desirable immune response, none of the cited references, either alone or in any combination, renders obvious the instantly claimed combination vaccines. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 16-20 and 22.

Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the cancelled claims, the claims as originally filed, and any other claims supported by the specification. Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,

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